TWO LECTURES

ON

THE CONNECTION BETWEEN THE CHEMICAL PROPERTIES AND THE PHYSIOLOGICAL ACTION OF ACTIVE SUBSTANCES;

AND

THE ANTAGONISM BETWEEN THE ACTION OF ACTIVE SUBSTANCES.

Delivered before the Royal College of Physicians, Edinburgh, on the 19*th and* 26*th of March*, 1872.

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LECTURE I.

ON

THE CONNECTION BETWEEN THE CHEMICAL PROPERTIES AND THE PHYSIOLOGICAL ACTION OF ACTIVE SUBSTANCES.

MR. PRESIDENT AND GENTLEMEN,—In addressing those who possess some familiarity with the subject I have the honour to bring before you, it is scarcely necessary to make the statement that a connection exists between the chemical properties and the physiological action of substances. The slightest effort of memory, or, at most, a glance at a table of elementary substances or list of chemical compounds, is sufficient to convince any one of the truth of this statement. For, among the numerous elementary substances or chemical compounds whose action has been investigated, it is difficult, if not impossible, to find two that possess exactly the same physiological action—that produce the same train of symptoms, and modify the functions of the same histological elements in the same way and with the same activity. Now, as one elementary substance is distinguished from every other elementary substance by the possession of certain distinctive chemical properties, and as one compound substance is likewise distinguished from all other compound substances by the possession of certain special chemical properties, it is obviously suggested that a relationship exists between the chemical properties and the physiological action of active substances.

Substances resembling each other in chemical properties possess actions that resemble each other.—No doubt, analogies, often of a close and striking description, occur between the physiological actions of different substances ; but these analogies tend to bring more distinctly into view the relationship referred to, by shewing that similar physiological effects are often produced by substances which resemble each other in many of their chemical properties. For instance, the various salts of

potash in a remarkable manner paralyse the heart's action, those of ammonia accelerate the circulation and produce spasms and general convulsions; and, indeed, the general truth of the proposition, enunciated by Dr. Blake in 1839—to which, however, there are several exceptions—that the salts of the same base have analogous actions, is now universally recognised. To the industry of this observer we are also indebted for another general proposition of great interest which bears upon this relationship. Several chemical substances possess the property of crystallising in the same form, and of replacing each other in crystalline compounds without alteration of the characteristic geometrical figure; in other words, they possess the property of isomorphism. The physiological action of a large number of inorganic substances belonging to different isomorphic groups has been examined by Dr. Blake. The symptoms that were observed have led him to believe that, with a few exceptions, a striking analogy exists between the isomorphic relations and the physiological action of the substances examined, an analogy to which he has given expression by the statement that "isomorphous substances produce similar effects."

Substances which resemble each other in certain of their chemical properties, possess similar degrees of poisonous activity.—Not only is there evidence to show that substances which resemble each other in their chemical properties may possess physiological actions of a similar kind, but a correspondence may likewise be traced between certain of the chemical properties and the physiological activity, or poisonousness, of substances. The combining or atomic weight of elementary bodies forms an important character by which they may be distinguished from each other, and Dr. Rabuteau has published an extensive and valuable series of experiments, which he had undertaken for the purpose of determining whether any relationship exists between the atomic weight and physiological activity of elementary bodies. As a result of this investigation, he has found that *the metals are more active physiologically according as their atomic weights are more elevated.* For example, in reference to sodium, potassium, and thallium: sodium, with an atomic weight of 23, is almost inert; potassium, with an atomic weight of 39, is active in moderate doses; and thallium, with an atomic weight of 204, is a dangerous poison, nearly as poisonous, indeed, as lead, whose atomic weight is 207. On comparing magnesium, zinc, and cadmium, it is seen that magnesium, with an atomic weight of 24, is scarcely more active than sodium (23), for the salts of the former are prescribed in about the same doses as those of the latter; while zinc, with an atomic

weight of 65, is a dangerous substance, although much less so than cadmium, whose atomic weight is 112. In reference to the metalloids, Dr. Rabuteau has found that those which are *diatomic*, as oxygen, sulphur, selenium, and tellurium, conform to the same law as the metals. The monatomic metalloids, however, are governed by a law which is the reverse of this; a fact which had previously been pointed out by Bouchardat and Stuart Cooper, who observed that chlorine (35·5) is more active than bromine (80), and the latter more so than iodine (127).

By changing the chemical properties of a substance, we may modify the physiological action.—These various facts show that resemblances between the chemical properties of substances may be accompanied with certain similarities in their physiological action and activity. The support that is thus given to the theory of a relationship between chemical property and physiological effect, is greatly strengthened when we find that the physiological action of substances may be modified by changing their chemical properties. Among the many examples that might be brought forward in illustration of such change, one of the most remarkable is that afforded by amygdalin. This neutral principle is derived from bitter almonds, and it is a substance that is devoid of physiological activity. There occurs along with it in the bitter almond, another principle, emulsin, which also is a substance that possesses no physiological activity. A large dose either of amygdalin or of emulsin alone may be injected into the circulation of an animal without any effect whatever being produced. When, however, the two substances are together injected, even at points far removed from each other, physiological effects are produced with great activity, and death occurs. The originally inert amygdalin has become a powerful poison, and this change is the result of a modification in its chemical properties—a modification which you will easily recognise by comparing the odour of the moistened amygdalin with that of the mixture of amygdalin, emulsin, and water, which I now place before you, and which may be represented by the equation:—

$$\underset{\text{Amygdalin.}}{C^{20}H^{27}NO^{11}} + 2H^2O = \underset{\substack{\text{Hydride of}\\ \text{Benzole.}}}{C^7H^6O} + \underset{\text{Prussic acid.}}{CNH} + \underset{\text{Glucose.}}{2C^6H^{12}O^6}$$

Another example of a similar kind, which may be here adduced, has been made known within recent times by the chemical researches of Matthiessen and Wright, and the physiological observations of Drs. Gee and Pierce, and others. The two chemists whom I have here named, in the course of their elaborate researches on the opium-alkaloids, found

that when morphia was acted upon by hydrochloric acid at a high temperature its chemical properties are modified, and its composition changed so that one equivalent of water is separated from it. The action of morphia thus modified has been examined, and it has been ascertained to possess a physiological action very different from that of morphia itself. In place of producing hypnosis, this changed morphia—to which the name of apo-morphia has been given—acts as a powerful emetic substance, so powerful, indeed, that in man emesis occurs within a very few minutes after the one-thirteenth part of a grain, or even a smaller dose, has been subcutaneously injected.

The general law, that the physiological action of a substance may be modified by changing its chemical properties, is, indeed, one whose truth is widely recognised in medical science. On it has been founded the application of chemical antidotes for poisons ; that is to say, of substances that modify the physiological effects of substances by changing their chemical properties. The chemical properties of arsenious acid are changed by hydrated sesquioxide of iron or by magnesia, those of tartar emetic by tannin or albumen, those of lead by sulphate of magnesia, those of prussic acid or soluble cyanides by proto and persalts of iron, those of oxalic acid by carbonate of lime, and those of morphia, strychnia, and various other alkaloids by tannin or iodine ; and as a result of this change the physiological properties of these substances are modified.

To the recognition of this law, likewise, therapeutics has become indebted for the introduction of a remedy which everyone must admit has proved of the greatest value in the treatment of disease. Although chloral was discovered more than thirty years ago, it was not until 1869 that Liebreich ascertained its important physiological action. The belief that a certain change in its chemical properties would enable it to produce a well defined physiological action, induced Liebreich to investigate the action of this substance. I need hardly say that the chemical change anticipated was the decomposition of the chloral, after its introduction into the circulation, by the alkaline salts present in the blood. This decomposition may readily be seen by adding, as I now do, some caustic alkali to a tolerably strong solution of chloral hydrate ; the result being the precipitation of minute globules of chloroform and the simultaneous formation of formiate of the base that is added :—

$$\underset{\text{Chloral}}{C^2\,Cl^3\,H\,O} + K\,H\,O = \underset{\text{Chloroform.}}{C\,Cl^3\,H} + \underset{\text{Formiate of Potassium.}}{C\,O^2\,K\,H}$$

The physiological action of an active substance may be accompanied with obvious chemical reactions between it and certain of the constituents of vital structures.—The principle which I am now endeavouring to illustrate, namely, that a connection exists between the chemical properties and the physiological action of active substances, receives a further and obvious support from several well-known facts, which show that the physiological action of active substances may be accompanied with distinct chemical reactions between them and certain of the vital structures. Thus, in producing its violent corrosive action, sulphuric acid withdraws the element of water from the tissues, liberates the carbon of their ternary hydrocarbons, and separates from them their basic constituents. The analogous corrosive effects of nitric acid are accompanied with the oxidation of tissue-elements, and combinations with electro-positive substances, and with the formation of xanthoproteic acid—by the last of which reactions the characteristic orange staining of the skin and fibrous tissues is caused. It is needless to point out how the local effects of the caustic alkalies are also accompanied with well-defined chemical changes in the vital structures on which they act.

One of the most striking examples of a definite change of chemical property accompanying the physiological action of a substance is that afforded by carbonic oxide. You are aware that this gas is largely present in the fumes of burning charcoal, and that it acts as a violent poison. Its special effects have formed the subject of a well-known investigation by Claude Bernard—an investigation that marks an era in the history of pharmacology. This distinguished physiologist discovered that carbonic oxide renders the blood of a marvellously florid colour, that it thrusts out oxygen from that fluid, and that its action is in some way related to the latter effect. More recent investigations, especially those of Lothar Meyer and Hoppe Seyler, have confirmed Claude Bernard's results, and also shown that carbonic oxide forms a definite chemical union with the hæmoglobin of the blood. The resulting compound is one of great stability; so much so, that carbonic-oxide-hæmoglobin resists the action of powerful reducing agents. The connection of these results with the action of this substance is easily seen. The physiological action is the direct result of the change in the chemical properties of hæmoglobin—a change which has, among other effects, that of preventing those chemical interchanges between it and the oxygen of the air on which life depends. The relation of the great stability of the combination between carbonic oxide and hæmoglobin to certain of its physiological effects is also apparent, for the serious symptoms which

are produced by the most minute quantity can be recovered from but slowly. They can, however, be recovered from ; and again we find that a chemical explanation may be adduced for this physiological change, as it has been recently discovered that, under the prolonged influence of oxygen, the carbonic oxide is at last liberated from its combination with the hæmoglobin.

There is some reason for supposing that somewhat similar chemical effects are produced during the action of prussic acid ; and it has been shown by the careful and elaborate observations of Dr. Gamgee that nitrites conduct themselves towards hæmoglobin in an analogous manner to carbonic oxide—a fact which may explain certain of the phenomena produced by nitrite of amyl.

Gentlemen, these various illustrative examples are, I think, sufficient to convince you that there are good reasons for supposing that *resemblances between the chemical properties of substances may be accompanied with certain similarities in their physiological action and activity; that the physiological action of many substances may be modified by changing their chemical properties; and that the physiological action of a substance may be accompanied with distinct chemical reactions between it and certain of the vital structures.* It is on these generalisations, and the facts by which they are supported, that the belief in a connection between the chemical properties and the physiological action of active substances has in all probability been originated.

Various attempts have been made to determine on what special chemical properties the physiological action of substances depend ; and I have had occasion to refer to several of these attempts, of which those of Blake and Rabuteau are undoubtedly the most important. It is also worthy of mention, that Dr. Broadbent of London has advanced the opinion, supported by many ingenious arguments, that the physiological action of a substance is related to a property which he terms *chemical tension*, and defines as the amount of energy developed by any possible rearrangement of the constituents of the substance ; while Dr. Benjamin Richardson has shown that, in a series of bodies belonging to the same chemical type, the character of the symptoms somewhat depends on the volatility and solubility of the various members of the series. It is not necessary to occupy your time by discussing these theories. Whatever germ of truth they may contain, their value in indicating a connection between the chemical properties and the physiological action of active substances is a comparatively limited one. I prefer, therefore, to pass without further delay

to the consideration of some other investigations which bear upon this subject.

Before doing so, it is necessary to inquire on what the chemical properties of substances are dependent. It is quite obvious that these properties depend on the chemical *composition* and *constitution* of substances; the latter term implying the mode of arrangement of their constituents, or the way in which these constituents are united together.

Chemical Composition and Physiological Action.—There are numerous indications of a relation between the chemical composition of a substance and its physiological action. Thus, as I have already mentioned, the salts of the same base have generally a common action—a law that is departed from when the base is united to an acid which itself has a distinct action. Similarly, the compounds of the same acids with physiologically indifferent bases produce the same effects. When, however, we consider more fully the relationship between composition and physiological action, we fail to discover the cause of the peculiar action of substances in the presence and proportion of particular elements. Many substances having identically the same composition—termed by chemists isomeric—possess very different physiological actions. This, for instance, is the case with the isomeric series represented by oil of turpentine, oil of lemons, oil of juniper, etc., all of which have the composition $C^{10} H^{16}$; and with that represented by nitrite of ethyl and glycocol, both of which have the composition $C^2 H^5 NO^2$. Kakodylic acid likewise very well illustrates the insufficiency of composition alone as an explanation of physiological action; for, although it is a soluble substance, and contains more than 54 per cent. of metallic arsenic, it may be administered in large quantities without producing any effect whatever. And, finally, the action of the organic alkaloids is obviously opposed to this explanation—an opposition which becomes apparent when we consider that aconitia paralyses the spinal cord, and also the inhibitory cardiac ganglia; while strychnia increases the activity of the reflex apparatus in the cord, and stimulates rather than paralyses the cardiac vagi nerves, although both substances are alike composed of carbon, hydrogen, nitrogen, and oxygen.

Chemical Constitution and Physiological Action.—The chemical properties of substances, however, depend not only on their *composition*, but also on their *constitution*. I have already said that the chemical constitution of a substance is the mode in which its constituents are arranged or united together. The difference between composition and constitution may be explained by a reference to such substances as the compound

ethers. They are formed by the action of an acid on an alcohol, and may be so decomposed as to yield again the alcohol and acid from which they were produced. Now, common alcohol ($C^2 H^6 O$) and valerianic acid ($C^5 H^{10} O^2$) have together the same composition as amylic alcohol ($C^5 H^{12} O$) and acetic acid ($C^2 H^4 O^2$) together. The combination of each of these two pairs of substances gives rise to a compound ether of identically the same composition, but differing in properties; and each of these compound ethers can be decomposed so as to yield the pair of substances from which it was produced. Thus,

$$\underset{\text{Common alcohol.}}{C^2 H^6 O} + \underset{\text{Valerianic acid.}}{C^5 H^{10} O^2} = H^2 O + C^7 H^{14} O^2$$

$$\underset{\text{Amylic alcohol.}}{C^5 H^{12} O} + \underset{\text{Acetic acid.}}{C^2 H^4 O^2} = H^2 O + C^7 H^{14} O^2$$

The one ether obviously differs from the other in the manner in which the constituents are united together; that is to say, in its constitution.

It appears, therefore, that substances may possess physical, chemical, and physiological properties that do not depend on their special composition. This independence of composition and property is also met with among inorganic substances. Some elements form only one series of compounds—as zinc with its single oxide, chloride, and sulphate. Other elements form more than one series—as iron with its proto- and per-salts, arsenic with its arsenites and arsenates, and sulphur with its sulphides, sulphites, and sulphates; and distinct physical and chemical properties are possessed by each individual series. In the examples which I have last mentioned, the investigation of the physiological action of the compounds belonging to any special series is a matter of considerable difficulty. Where varieties of constitution exist, the compounds of the less stable varieties readily undergo decomposition, and assume that constitution which possesses the greatest stability. Thus the proto-salts of iron easily change their constitution, and become converted into per-salts; and arsenates become reduced to arsenites. That changes of constitution also occur in the body, has been rendered certain by numerous observations, and more especially by those of Rabuteau, who has shown that, when introduced into the system, bromates become changed to bromides, iodates to iodides, and sulphites and hyposulphites to sulphates: in fact, that towards these substances the organism acts as a reducing agent. Hence, there is an absence of definite knowledge regarding the action of more than one series of the compounds of the elementary bodies.

Among the organic compounds, however, a large class of substances may

have their constitution modified in such a manner that a change to the original or any other form is effected only with the greatest difficulty. The substances to which I refer are the natural alkaloids. Their constitution is not fully known ; but it is sufficiently known to prove it to be of the same type as that of ammonia, and to show that they resemble that substance in containing triatomic nitrogen. Thus, ammonia = $N\left\{\begin{array}{l}H\\H\\H\end{array}\right.$; strychnia = $N \equiv (C^{21}\,H^{22}\,NO^{2})'''$. Like ammonia, also, they are converted by union with acids into salts having a different constitution—a constitution in which the nitrogen, in place of being triatomic, becomes pentatomic. For instance, in the formation of hydrochlorate of strychnia, the originally triatomic nitrogen takes up chlorine and hydrogen, and becomes pentatomic, $N\left\{\begin{array}{l}(C^{21}\,H^{22}\,NO^{2})'''\\H\\Cl\end{array}\right.$, united by three bonds to carbon, by one to hydrogen, and by one to chlorine ; just as the triatomic nitrogen of ammonia unites itself by two additional bonds to chlorine and hydrogen, and so becomes pentatomic in hydrochlorate of ammonia, $N\left\{\begin{array}{l}H\\H\\H\\H\\Cl\end{array}\right.$. But, by this change, hydrochlorate of strychnia is not rendered permanently or stably pentatomic ; it easily loses the chlorine and hydrogen which it has acquired, and returns to the triatomic state. The action of alkalies, or, in many cases, even of alkaline carbonates, is sufficient to effect this, and to set free the alkaloid. It is obvious, therefore, that the change of constitution effected by the addition of an acid does not permit us to discover the corresponding change in physiological action. But if, instead of an acid, we make use of such a substance as iodide of methyl, we find that, while the triatomic nitrogen takes up methyl ($C\,H^{3}$) and iodine, and becomes pentatomic (just as in the former case it took up hydrogen and chlorine), it does not lose these newly acquired atoms when treated with alkalies, but remains pentatomic even when subjected to attacks more violent than any to which it could be exposed in the system.

I have alluded to the type of the natural alkaloids being that of ammonia, but certain varieties of constitution are met with, to which I would now draw your attention. In ammonia, the nitrogen is united

to three equivalents of hydrogen. Now, one or two or three of these equivalents may be replaced by one or more radicals, and in this way we have amine, imine, and nitrile bases. Thus, one equivalent of hydrogen is replaced by $C\,H^3$ in the amine base, methylamia, $N\left\{\begin{matrix}(CH^3)' \\ H \\ H\end{matrix}\right.$; two equivalents by the diatomic radical $(C^8\,H^{14})''$, in the imine base, normal conia, $N\left\{\begin{matrix}(C^8\,H^{14})'' \\ H\end{matrix}\right.$; and three equivalents, by the same diatomic radical, and by $C\,H^3$, in the nitrile base, methyl-conia, $N\left\{\begin{matrix}(C^8\,H^{14})'' \\ C\,H^3\end{matrix}\right.$, or, to take another example of a nitrile base, by one equivalent of the triatomic radical $(C^{21}\,H^{22}\,N\,O^2)'''$, in strychnia, $N \equiv (C^{21}\,H^{22}\,N\,O^2)'''$. These various bases are distinguished from the bases derived from them in which nitrogen is stably pentatomic (called ammonium bases) by certain chemical characters common to them all. Their salts, for instance, are decomposed by caustic potash, so that the base is set free, and water and a salt of potassium formed; and a similar effect is produced by moist oxide of silver. The salts of the ammonium bases, however, are not acted upon by caustic potash, and, when treated with moist oxide of silver, a hydrated oxide of the ammonium base (in which nitrogen remains pentatomic) is formed, and the acid unites with the silver.

The powerful decomposition action which caustic potash is able to exert does not, therefore, change the chemical constitution of these ammonium bases. It, indeed, has no effect upon their salts; and even when these salts are treated with moist oxide of silver the characteristic pentatomicity of their nitrogen is retained. In the living body, they cannot possibly be subjected to the influence of such powerfully decomposing agents; and hence, by studying their action, and comparing it with that of the nitrile or other base from which they are derived, the relationship between physiological action and a certain form of chemical constitution may be discovered.

It was owing to this consideration that Dr. Crum Brown and I resolved to examine the action of a number of the ammonium bases derived from the vegetable alkaloids. Our experiments were made with the methyl, and, in a few instances, the ethyl, derivatives of strychnia, brucia, thebaia, codeia, morphia, nicotia, atropia, and conia, and more especially with their iodides and sulphates.

The results that we obtained may, perhaps, be best illustrated by de-

scribing, with a little detail, several of our experiments with iodide and sulphate of methyl-strychnium.

It is well known that strychnia acts on the living economy in a distinctly defined and characteristic manner, and that it is one of the most active of poisons. When administered subcutaneously, doses varying from one-twentieth to one-fiftieth of a grain produced in rabbits the most violent tetanic convulsions, and in a few minutes killed the animal. Few poisons have been more carefully studied, and it is now almost undoubtedly established that the phenomena produced by strychnia are due to a localisation of its action on the spinal cord.

The effects of iodide of methyl-strychnium were first examined by subcutaneous injection. It was administered as a fine powder suspended in warm distilled water, in which menstruum it is but sparingly soluble, though more so than in water at the ordinary temperature. In this way, by a series of progressively increasing doses, it was found that as much as twelve grains could be given to a rabbit, weighing three pounds, without any effect whatever. Fifteen grains, however, produced serious symptoms, though followed by recovery; and death was caused by the administration of twenty grains. In none of our experiments, not even in the fatal cases, were the symptoms those of strychnia-poisoning; no starts nor spasms occurred, nor did stimulation give evidence of the slightest increase of reflex activity. In fact, a condition exactly the reverse of that produced by strychnia was caused by iodide of methyl-strychnium. In place of violent spasmodic convulsions and muscular rigidity, the appearances were those of paralysis with a perfectly flaccid condition of all the muscles. The limbs of the animal first yielded; its head gradually sank until it rested on the floor; by-and-by, it lay in a perfectly relaxed condition; and when death occurred, it was due to stoppage of the respiratory movements. In the necropsies, further evidence was obtained to distinguish the effects of iodide of methyl-strychnium from those of strychnia. The heart was found acting with nearly its normal rapidity; the spinal motor nerves were either paralysed, or nearly so; and, in place of the early or almost immediate occurrence of rigor mortis that follows the action of strychnia, the muscles continued flaccid, contractile, and alkaline for many hours.

The effects of internal administration were examined by passing a gum-elastic catheter down the œsophagus of a rabbit, and so injecting iodide of methyl-strychnium, suspended and dissolved in warm distilled water. It is unnecessary to give any description of these ex-

periments, as no effect was produced by this method of administration, although as much as thirty grains was given at one time ; and it was inconvenient, as well as unnecessary, to give larger doses. It is well known that to produce symptoms with a poison in a rabbit, a much larger quantity is required when the poison is administered by the stomach than when it is injected subcutaneously. The contrast between the activity of iodide of methyl-strychnium and strychnia itself was, however, well shown in the rabbit to which thirty grains of the former had been given without any effect; for one-tenth of a grain of strychnia, also administered by the stomach, quickly produced violent tetanic convulsions, and in a few minutes killed the animal.

As the sulphate of methyl-strychnium is a very soluble salt, we anticipated that it would act with much greater activity than the iodide, and our experiments confirmed this anticipation. One grain dissolved in water and injected under the skin of a rabbit caused its death in eighteen minutes. Half a grain, however, produced no marked effect. When eight-tenths of a grain were similarly administered, symptoms of a most serious character were produced, but death did not result. Some days afterwards, one-twentieth of a grain of strychnia, dissolved in very dilute sulphuric acid, was administered to this rabbit by subcutaneous injection ; and it produced symptoms of strychnia action, followed by death fifteen minutes after the injection. Eight-tenths of a grain of sulphate of methyl-strychnium contain about six-tenths of a grain of strychnia : the effect of converting this nitrile base into an ammonium base by adding to it sulphate of methyl had been, therefore, to reduce its poisonous activity at least twelve times.

The symptoms that are produced by sulphate of methyl-strychnium are the same as those produced by the corresponding iodide. The very short account I have given of the symptoms and *post mortem* appearances that occur after the administration of iodide of methyl-strychnium is sufficient to suggest a close resemblance between its action and that of curara (wourali)—a resemblance, indeed, which had previously been pointed out by Professor Schroff, of Vienna. Both substances undoubtedly produce a condition of general paralysis, but the special characteristic of curara-poisoning is that this paralysis results from an impairment or destruction of the function of the peripheral terminations of the motor nerves. It is impossible to demonstrate such an action without undertaking experiments of a special character. Dr. Brown and I accordingly extended our research for the purpose of studying the exact causation of this paralysis.

Among other experiments, we made the following. The sciatic artery and veins were tied above the knee of a frog, and a small dose of sulphate of methyl-strychnium, dissolved in water, was injected under the skin at the back. Eight minutes afterwards, the frog was lying in a perfectly flaccid state ; and, in ten minutes, irritation of any portion of the skin produced energetic movements of the tied limb below the point of ligature, but nowhere else. The sciatic nerve of the untied limb was now exposed, and on stimulating it with a weak, interrupted, galvanic current, movement occurred in the tied limb only ; not the slightest movement occurred in any part to which the poison had access. At the same time, the muscles were everywhere active, and freely contracted when directly stimulated. The sciatic nerve was then exposed in the tied limb, above the points of ligature, and on stimulating it energetic movements occurred below the knee of that limb, and there only. The heart at this time was acting at the rate of 50 per minute.

This experiment was frequently repeated—on several occasions the iodide having been substituted for the sulphate—and the same general results were obtained. The evidence that was thus acquired in favour of an action on the peripheral terminations of the motor nerves, was strengthened by a modification of the experiment.

The right gastrocnemius muscle of a frog was carefully dissected from its connections ; excepting that its origin and insertion, and the nerves entering it, were uninjured, and that all its blood-vessels were ligatured. A small dose of sulphate of methyl-strychnium, in solution, was then injected under the skin of the back ; twenty minutes afterwards, the animal being in a perfectly motionless and flaccid condition, the two sciatic nerves were exposed. Galvanism of the left produced no movement of the left limb, while galvanism of the right produced energetic movements of the right limb, which were seen to be due solely to contractions of the right gastrocnemius muscle, the other muscles remaining motionless. At the same time, direct stimulation caused contractions as freely in the poisoned muscles as in the non-poisoned right gastrocnemius.

In experiments where iodide of methyl-strychnium was substituted for sulphate, the results were the same. The methyl derivatives of strychnia, therefore, produce paralysis and death, by destroying the function of the peripheral terminations of the spinal motor nerves. Accordingly, their mode of action is identical with that of curara. This result is an extremely curious and interesting one. It is difficult

to imagine a more decided modification in the action of any substance than is produced by the change of chemical constitution resulting from the addition of iodide or sulphate of methyl to strychnia. The striking characteristic of the action of strychnia is the great and uncontrollable activity of the muscular system; that of curara, of iodide and sulphate of methyl-strychnium, and, as we also found, of other similarly modified alkaloids, is the flaccid and motionless condition caused by the impossibility of exciting muscular action through the nervous system. So opposite are their effects, that many physiologists look upon curara as a powerful counter-agent to strychnia, while physicians have employed it in the treatment of strychnia-poisoning and of tetanus. It is certainly remarkable that so thorough a change of physiological action should be produced by this simple change of chemical condition.

The other vegetable alkaloids examined, all possess, though in varying degrees, the same peculiar spinal-stimulant action as strychnia. Brucia and thebaia exert this action with great energy; codeia and morphia with somewhat less power; and nicotia, atropia, and methyl-conia, in a still slighter degree, though quite obviously. The result of the combination of each of them with a salt of methyl being, as in the case of strychnia, to change their chemical constitution from that of nitrile bases with triatomic nitrogen, to stable ammonium bases with pentatomic nitrogen; and the change of physiological action following this change of chemical constitution having been found to consist of a removal of spinal-stimulant action and addition of paralysing action restricted to the terminations of the motor nerves, it is unnecessary to give any further details of the results of our experiments. The important general fact which they indicate is, that a change of chemical constitution, even when it is of a simple kind, may produce a very essential change in physiological action; and, although they are perhaps as yet insufficient to warrant any positive assertion, they render it extremely probable that all the stable ammonium bases have a curara-like action. Every such compound that has as yet been examined has been found to possess this action. To the list of those which I have mentioned may be added chloride of oxethyl-strychnium—recently studied by Dr. Vaillant—and iodide of tetra-ethyl-phosphonium—which has formed the subject of a careful investigation by Dr. Vulpian—both salts of ammonium bases, and both found to possess a powerful action on the terminations of the motor nerves.

I am anxious, however, to guard against conveying the impression that the compounds of pentad nitrogen act simply as nerve-paralysers

their action is not necessarily restricted to these structures. In several cases it is, no doubt, so restricted; and notable examples of this are found in the salts of methyl-strychnium, methyl-brucium, and methyl-thebaium, whose nitrile bases have probably no other decided action than a spinal-stimulant one. In those cases, however, in which the salts of ammonium bases are derived from alkaloids that produce complicated effects, a restriction of action to the terminations of the motor nerves does not occur. The original actions of the alkaloid, excepting the spinal-stimulant one, are retained by the salts of its ammonium base; and thus the salts of methyl-atropium not only act like curara, but they likewise paralyse the cardiac inhibitory fibres of the vagi and dilate the pupils, while the salts of dimethyl-conium retain the paralysing action on the vagi that is possessed by conia itself.

In considering how these various facts bear upon the connection between chemical constitution and physiological action, it is no doubt essential to remember that a change of composition as well as of constitution has been produced by the conversion of the nitrile into the ammonium bases. In the substances examined by Dr. Brown and myself, the composition of the original alkaloids was changed by adding to them a salt of methyl. Are, then, the subsequent changes of physiological effects produced by the action of the added salt of methyl? This hypothesis is so improbable as scarcely to deserve consideration. It is opposed by the experiments made with iodide of tetra-ethyl-phosphonium, to which I have already alluded; for this, also, is the salt of an ammonium base, which, however, differs greatly in composition from any of the substances examined by Dr. Brown and myself, although it exerts the same physiological action. It is opposed, also, by the results of experiments with conia and its derivatives; for the hydrochlorate of the nitrile base (methyl-conia), formed by the addition of hydrochlorate of methyl to the imine base (normal conia), exerts, notwithstanding this addition of methyl, a more marked spinal-stimulant action than normal conia, into whose composition methyl does not enter; while the salts of the ammonium base di-methyl-conium have a prominent curara action, and no spinal-stimulant action whatever. Besides, the action of iodide of methyl itself does not give the least support to this idea—for its effects are those of a powerfully irritating substance, and its action, even when induced by subcutaneous injection, results in inflammation of the bronchial mucous membrane and coma, and not in paralysis of motor nerves.

It might also be asked, if the processes by which these ammonium

bases are prepared do not so profoundly modify the chemical nature of the alkaloids from which they are derived, that no actual relationship exists between the new substances and their original sources; that, for example, sulphate of methyl-strychnium, though derived from strychnia, is in no special manner related to sulphate of strychnia—the elements of the latter substance having been so disarranged in its conversion into the former, that the strychnia has been altogether destroyed. It is, I think, a sufficient answer to this conjecture to point out that the ordinary colour reactions of the alkaloids are retained by their methyl derivatives.

Gentlemen, the various facts which, in a somewhat discursive manner, I have now brought before you, confirm the opinion that chemical composition bears some relation to the physiological action of active substances, and they also prove that this relationship is to an important extent due to the arrangement of the atoms in the substance. They appear, likewise, to point to the conclusion that physiological action is often, if not always, the result of a chemical reaction between the foreign body and certain of the constituents of the vital structures whose action is modified by it. The results of investigation with such substances as carbonic oxide, show, indeed, that physiological action may be chiefly the result of chemical reactions. The effects of other substances have not been connected with chemical action in so direct a manner, but this is to a great extent explainable by the difficulties attending the demonstration of a connection of this kind. Although experimental research, in many cases, has discovered the exact histological elements which are acted upon, the chemical characters of these elements have not yet been sufficiently ascertained. We have no means of determining their normal conditions with the delicacy that is required, and we are, therefore, unable to investigate the chemical reactions that almost certainly accompany modifications of their normal physiological condition during the operation of active substances. Thus, although we know that the normal physiological condition of the terminations of motor nerves are modified by the salts of the ammonium bases derived from strychnia, brucia, thebaia, etc., and that this modification is produced by substances that have definite chemical properties, we cannot discover what chemical change is produced so long as we are ignorant of the special chemical properties possessed by these structures. The trustworthy observations of Kühne have shown that a recognisable change occurs in the physical characters of the nerve terminations—a change which renders their outlines

more distinct; but we are unable to connect this change with any definite chemical reaction. In the course of time, reactions of a more delicate kind than any we yet possess will, no doubt, be discovered, not only for these structures, but likewise for each of the special structures on which the physiological action of active substances is localised. Physiological investigation has shown that one substance may chiefly exert its influence upon the cardiac inhibitory ganglia, another on the nerve-fibres intermediate between these ganglia and the ends of the vagi nerves, and another on these endings themselves. How are these localisations of action to be explained? There must undoubtedly be a difference between the chemical properties of each of the structures influenced. The discovery of the spectroscopic characters of hæmoglobin has greatly extended our knowledge of the action of such substances as carbonic oxide, by placing at our disposal a means of defining the chemical reactions that take place between it and the blood. In giving expression to the anticipation that similarly delicate tests of chemical reaction will yet be discovered for each of the special histological elements of the body, I do not think that we err by being too sanguine. Were such means of investigation at our disposal, it may safely be predicted that knowledge would be acquired of as perfect a kind as is indicated in the following quaint sentence, written by Locke: "Did we know the mechanical affections of the particles of rhubarb, hemlock, opium, and a man, as a watchmaker does those of a watch, whereby it performs its operations; and of a file, which, by rubbing on them, will alter the figure of any of the wheels, we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep." It is encouraging to find that even now we know of certain "affections of the particles" of active substances which enable us to tell beforehand that, wherever these affections occur, well defined and characteristic physiological effects will be produced.

LECTURE II.

ON

THE ANTAGONISM BETWEEN THE ACTIONS OF ACTIVE SUBSTANCES.

MR. PRESIDENT AND GENTLEMEN,—When I was honoured by the request to bring under your notice some subjects bearing upon pharmacology, I found myself placed in the difficult position of having too many good things to choose from. Within my reach were the fruits—seldom altogether ripe, but without exception temptingly attractive—of numerous investigations, conducted both in this country and abroad, in the field of pharmacological research. At my disposal, also, were the methods by which these fruits had been cultivated—the refinements of experimentation, and the mechanical appliances by whose aid, within recent years, results of surpassing beauty and interest have been obtained, and much progress has been made in the establishment of a sound basis for therapeutics. The consideration of either of these subjects, however, would have required much more time than could be found within the limits of two lectures. It was for this reason that I selected two subjects that admit of briefer discussion, while at the same time they possess a sufficiently independent interest to allow of their being treated apart from the general subject in which they are included.

Definition of Antagonism.—The connection between the chemical properties and the physiological action of active substances occupies a position on the border-land of pharmacology, for it is placed between pharmacology and one of the sciences most intimately related to it. The subject which I propose this evening to bring before you is placed, on the contrary, in the centre of this region, seeing that it is chiefly concerned with the relationships that exist between different groups of well defined pharmacological facts.

Presupposing a definite knowledge of the modifications produced in normal physiological conditions by a certain number of active substances to have been acquired, antagonism is concerned with the opposing influence which the action of one or more of these substances is able to exert upon that of any of the others—with the opposing actions, for example, of morphia and atropia on the pupils and minute blood-vessels, of morphia and quinia on the circulation, of prussic acid and atropia on the vagi nerves, and of physostigma and atropia on the iris and on visual accommodation. When several of the actions of one substance are counteracted by those of another, the antagonism becomes a more general one than in the examples I have cited; and when, among the different counteracting actions that occur in general antagonism, there are included any by which the fatal effect of one or other of the substances is usually produced, the one substance may act towards the other as a physiological antidote.

Physiological antidotism is, therefore, a very different thing from chemical antidotism. In all probability, however, the origin of the one may be referred to the same cause as that of the other. Soon after it became known that injurious effects follow the introduction of certain substances into the system, attempts were naturally made to remedy these effects, and also to discover counteragents or antidotes to the hurtful substances. The success attending these attempts was of necessity closely related to the existing state of knowledge regarding the physiological action and the physical properties of active substances. When the effects of poisons were referred to supernatural manifestations, it was chiefly charms and superstitious rites that were trusted to as protectives and remedies. At a somewhat more advanced period in the progress of human knowledge, vague notions of physiological laws and processes supplied the indications of curative treatment; and bezoars, alexipharmics, Mithridates, and theriacæ, were employed almost indiscriminately as universal antidotes. Still later, chemistry suggested that, as the physical properties of poisons may be modified by various reagents, so may their effects be prevented by the administration of suitable substances.

The recommendations derived from chemistry were at first only of the crudest description; but, as the science advanced, many valuable hints were obtained, and now the class of the chemical antidotes includes a large number of efficient counteragents to poisons. Their operation, however, appears to be limited to the chemical changes which they produce on the poison while it remains in the alimentary canal.

As soon as the poison becomes absorbed into the blood, it seems to pass beyond the antidotal influence of the chemical counterpoison; for no example exists of a chemical antidote neutralising a poison after absorption. This may be explained by the fact that the chemical antidotes known to us are never sufficiently stable bodies. Their affinities are numerous; and so, after their entrance into the blood, they dissipate the chemical energy on which their value depends by forming combinations with the elements of the blood and tissues, in place of reserving that energy until the absorbed poison is reached and neutralised.

Reputed Examples.—In order perfectly to neutralise the injurious effects that follow the introduction of active substances into the living economy, it would appear to be necessary that the physiological functions of the affected organism should be modified. The early though undoubtedly crude notions that originated the employment of alexipharmics, Mithridates, and theriacæ, to a certain extent recognised this principle. The two latter of these compounds contained opium, along with an immense number of other ingredients; and so their indiscriminate employment as antidotes may have led to the first suggestion, or at least to one of the earliest applications, of an antagonism whose recognition dates from a remote period of medical history. I refer to the antagonism between opium on the one hand, and belladonna, hyoscyamus, and stramonium, on the other. One of the earliest records of a belief in the existence of this antagonism is to be found in the *Stirpium Adversaria Nova*, published in 1570 by Pena and De Lobel, where the statement is made that some Italian pedlers, who gained much notoriety by employing the root of the belladonna-plant to quench thirst, were in the habit of administering opiates to remedy the evil effects that occasionally were thereby produced. Tracing the history of this antagonism down to the present time, we find that during the seventeenth and eighteenth centuries, and at the commencement of the present century, several cases were reported, more especially by Horstius, Faber, Boucher, and Joseph Lippi, in which opium was administered with apparent benefit in the treatment of poisoning by belladonna. Within more recent times, many modern authors, as Angelo Poma, Anderson, Cazin, Benjamin Bell, Behier, Lee, Norris, and Constantin Paul, have published evidence, derived from cases of poisoning in man, that appear to favour a belief in its existence. I need scarcely point out that evidence of this kind is usually surrounded by numerous causes of fallacy. It is not surprising, there-

fore, that observers of such recognised ability as Drs. John Harley and L. Orfila should have come to the conclusion, after a careful examination of the record of each case, that the evidence derived from clinical experience is insufficient to establish the reality of this antagonism ; or that Dr. Fraigniaud and others should besides assert that the association of opium with belladonna, in place of producing a diminution, produces an increase, of the toxic power of both substances. For my part, I feel inclined to believe that, while the existing evidence is insufficient distinctly to prove that opium is able to prevent the fatal effect of belladonna, hyoscyamus, or stramonium, or these latter substances that of opium, it is still sufficient to render it extremely probable that a general antagonism does really exist—to the extent, at any rate, of the primary lethal action of morphia being preventable by the physiological action of the other substances which I have named. A properly devised series of experiments would in all likelihood justify the opinion of those who, with no little courage, have practically affirmed their belief in the existence of this antagonism.

The rapid development of pharmacology has led to the acquisition of definite knowledge regarding the manner in which many active substances influence the physiological condition of vital structures ; and it has been found that the modifications produced by certain of these substances are of an opposite kind to those produced by others. In this way the existence of many instances of localised antagonism—to several of which I have already alluded—have been established.

The study of pharmacology has likewise led to the differentiation of the special structures by the modification of whose physiological conditions the lethal action of poisonous substances is produced. In a few instances, it has been shown that the nature of the modification produced in the physiological condition of the structure or structures involved in the lethal action of one substance, is apparently contrary to that produced on the same structure or structures by the physiological action of another substance. The establishment of such facts has led to the suggestion of various instances of antagonism, in which it is supposed that the lethal action of one substance may be prevented by the physiological action of another. Prominent among these are the antagonism between the lethal action of prussic acid and the physiological action of atropia, and that between the lethal action of muscaria and the physiological action of atropia. The elaborate researches of Preyer and of Schmiedeberg and Koppe proved that both prussic acid and muscaria increase the excitability of the vagi nerves, and in this way so

seriously affect the cardiac and respiratory functions, that death results when sufficiently large doses are given. Previous investigators—more especially Von Bezold and Bloebaum—had already discovered that atropia exerts an action that is in a remarkable manner contrary to that of these substances; for it paralyses the cardiac inhibitory fibres of the vagi, and likewise the terminations of these nerves in the lungs, and thus accelerates both the cardiac and respiratory movements. Guided by these facts, Preyer made a few experiments which strongly support the opinion at which he has arrived, that atropia is a physiological antagonist to prussic acid, even to the extent of being able to prevent the primary lethal action of that poison; while Schmiedeberg and Koppe have made several experiments which induce them to believe that the lethal action of muscaria may be counteracted by atropia.

In addition to these, many other examples of general or of lethal antagonism have been advanced. Their existence, however, has rarely been inferred from a knowledge that the substances concerned influence the same structures in contrary modes, but has been conjectured from a knowledge of merely the general phenomena that are produced by these substances. The conspicuous spasmodic effects by which the action of strychnia is characterised appear to have suggested the employment, as physiological counteragents, of various substances whose general action includes the production of paralysis; and accordingly the list of proposed antagonists to this alkaloid embraces opium, curara, aconitia, nicotia, bromide of potassium, chloroform, chloral, and nitrite of amyl. Opium and quinia have been proposed as antidotes to each other, on the supposition that the former exalts several of the organic functions, while the latter depresses them; and the physiological actions of iodine and bromine are said to neutralise each other, because the former substance produces sedation, and the latter excitation, of certain general functions.

Among these examples, there are several worthy of further examination; and it is not impossible that their existence may thereby be established. Meanwhile, the criticism of the Professor of Therapeutics at Paris, in reference to the majority of recorded examples of antagonism, appears to be a just one—that "la précision fait souvent défaut dans l'analyse des faits, les inductions manquent de rigueur, et la pratique attend de nouvelles lumières de la part de la physiologie expérimentale et de la thérapeutique rationnelle."

Chief Fallacies in the Evidence regarding the Existence of Antagonism.—This absence of precision may, I believe, with peculiar justice, be

said to characterise the evidence by which the existence of such general antagonism as enables one substance to prevent the lethal action of another has been supported. In nearly every instance, too much weight has been placed on a mere modification, or it may be amelioration, of the symptoms, while the establishment of the fundamental fact of these symptoms being the result of a lethal dose has not been sufficiently attended to.

It is doubtful whether, from clinical observation alone, a sufficient degree of precision can ever be obtained. Not only are there difficulties in the way of discovering what dose of poison has been introduced into the system, but even when this dose is ascertained, it is generally impossible to feel assured that it is a sufficient one to produce death. And, further, the effects of the substance administered as a physiological antidote can rarely be accurately observed. The exigencies of treatment demand that every likely method of alleviating the symptoms should be applied ; and, among the various remedial measures that are almost always applied, it is difficult, if not impossible, to discover accurately the effects of any single antidote.

How these Fallacies may be avoided.—The only method whereby the existence can satisfactorily be proved of an antagonism, so perfect as that which enables one substance to prevent the fatal effect of another, is by experiment on the lower animals. It is not necessary for me to attempt to show that the fallacies asserted to exist in such experiments have been greatly exaggerated, or that the supposed differences between the results obtained in man and in the lower animals do not possess the importance that has been claimed for them, as, fortunately, nothing remains to be done in this direction since the convincing arguments of Claude Bernard have been advanced and generally accepted.

By testing the existence of antagonism by experiments on the lower animals, the most important of the causes of fallacy to which I have alluded may readily be avoided. In any given species of animal, it is a simple matter to determine the minimum dose of an active substance that can produce death, and then to test the antidotal influence of its supposed antagonist after the administration of an undoubtedly lethal dose of the poison. In this manner, the most convincing proof may be obtained of an antidotal influence ; and, inspired with the confidence that is thus gained, the practitioner may with propriety employ the antidote in cases of poisoning in man.

The Antagonism between Atropia and Physostigma.—A plan of this kind was followed in a research which I lately undertook on the antag-

onism between atropia and physostigma. The experiments were chiefly performed on dogs and rabbits, to whom the substances were administered by subcutaneous injection; and their main purpose was to determine whether the fatal effect of physostigma can be prevented by atropia. Some of the results seem of sufficient interest to justify me in bringing them before you at this time.

In order to illustrate the effects that are produced by physostigma alone, let me, in the first place, describe the symptoms that occur when a lethal dose of the extract of this substance is given to a rabbit. Soon after such a dose is administered, infrequent and slight twitchings take place over the surface of the animal, and then movements of the mouth and lips occur, as if an accumulation of saliva were being removed. In the course of a very few minutes, there is evident difficulty in going about; gradually, stiff extension shows itself in the anterior, and then in the posterior, extremities; and thereafter the animal stumbles about, or stands shaking with the body elevated on the extended limbs. In a short time, the extended state of the limbs is succeeded by their partial paralysis; great weakness, accompanied with constant tremblings, is present; fluid escapes from the mouth, and soft and pultaceous fæces are passed at frequent intervals. The respirations become infrequent and laboured, and the heart's contractions diminished in their frequency and force; while the pupils contract below their normal size. Soon afterwards, the respiratory movements assume the character of mere laboured gasps, the pupils still further diminish in size, and general weak tremors succeed each other; while the flow of saliva, the discharge of semi-liquid fæces, and the incessant fibrillary twitches of the surface continue. By and by, it is a matter of difficulty to distinguish any respiratory movement or cardiac impulse, and they soon altogether cease on the occurrence of death.

Such a train of symptoms is usually produced by a dose of physostigma representing the smallest quantity that can kill a rabbit, and this event occurs in from twenty to thirty minutes. Let us now see how the effects of a considerably larger dose may be modified by atropia.

A rabbit received, by subcutaneous injection, a dose of extract of physostigma considerably greater than the minimum-lethal; and one minute and a half afterwards it received, also by subcutaneous injection, half a grain of sulphate of atropia. In three minutes after the injection of atropia, the pupils measured $\frac{14}{50} \times \frac{14}{50}$ths of an inch, the measurement immediately before the experiment having been $\frac{10}{50} \times$

$\frac{9}{50}$ths. In seven minutes, the pupils measured $\frac{10}{50} \times \frac{10}{50}$ths, the rate of the heart's contractions was considerably accelerated, fibrillary twitches were occurring, and a little restlessness was present. Soon afterwards, the pupils became still more dilated, and the animal had some difficulty in moving about. In twenty-five minutes, this difficulty had become greater—even to such an extent, that often the anterior extremities yielded, and the rabbit fell on the thorax. In fifty-two minutes, the pupils measured $\frac{15}{50} \times \frac{14}{50}$ths of an inch, but no obvious change had occurred in the general condition of the animal. In one hour and ten minutes, however, evidences of recovery were manifested ; the rabbit went about with but little difficulty, and frequently a perfectly normal sitting posture was assumed. Indeed, the only symptom of an abnormal character that was now apparent consisted of frequently occurring and well marked fibrillary twitches. From this time the condition of the animal steadily improved, until perfect recovery occurred.

Preliminary experiments had satisfied me that the dose of physostigma extract given in this experiment was at least twice as large as the minimum-lethal. Yet the fatal effect of this large dose was prevented in a remarkable manner by the dose of atropia that was given in conjunction with it. To add to the proof that was thereby obtained of an antagonism between these two substances, I administered to this rabbit, nine days afterwards, a dose of extract of physostigma only one half as large as that from which it had thus recovered. Symptoms of poisoning very quickly appeared, and death occurred in about fourteen minutes.

In another experiment on a rabbit, which I shall briefly describe, a lethal dose of sulphate of physostigmia was allowed to exert its action for a longer period than in the last experiment, before a dose of sulphate of atropia was administered. Previously to the administration of the physostigmia, it was found that the average rate of the cardiac contractions was 38, and that of the respiratory movements 22, in ten seconds; and that the pupils measured $\frac{11}{50}$ths by $\frac{10}{50}$ths of an inch. Fifteen minutes after the lethal dose of sulphate of physostigmia had been given, the rabbit was lying on the side, and saliva was flowing copiously from the mouth ; infrequent, laboured, and noisy respirations were occurring ; the cardiac contractions were extremely feeble, and at the rate of only nine in ten seconds ; and the pupils had contracted to $\frac{7}{50}$ths $\times$ $\frac{7}{50}$ths of an inch. In fact, the animal was at the point of death.

A marvellous change, however, was quickly produced by the ad-

ministration of sulphate of atropia. Two minutes after seven-tenths of a grain of this substance had been injected under the skin, the respirations were occurring at the rate of 18 in ten seconds, while their character was nearly normal; and the cardiac contractions were strong, and at the high rate of 50 in ten seconds, the rate before the antidote was given having been only nine in ten seconds. Soon afterwards, the pupils dilated and the flow of saliva ceased; and, by and by, the animal again turned from the side, raised the body on the limbs, and then assumed a perfectly normal posture. It was shown that the dose of sulphate of physostigmia from which this animal had recovered was a lethal one, by administering to it, several days afterwards, a dose of equal size, without any atropia. The usual symptoms of physostigma-poisoning were thereby produced, and death occurred in sixteen minutes.

I have said that the antagonism between atropia and physostigma was tested in dogs as well as in rabbits, and in order to illustrate the nature of this antagonism in the former animal, it may be proper to give a few details of one of my experiments. An active young Scotch terrier dog, weighing ten pounds and three ounces, received, by subcutaneous injection, three-fifths of a grain of sulphate of physostigmia, dissolved in a few drops of distilled water. Before the injection, the rate per ten seconds of the cardiac impulses was 32, and that of the respirations 4, and the size of the pupils, in a full light, was $\frac{12}{50} \times \frac{12}{50}$ths of an inch. In four minutes after the commencement of the administration, slight tremors occurred, and fibrillary twitches were present. In five minutes, a solution containing three-tenths of a grain of sulphate of atropia was injected under the skin. In two minutes thereafter, the tremors already noted had become more prominent and strong, the limbs were unable properly to support the body, saliva escaped from the mouth, and the eyeballs were unnaturally moist. In five minutes, the pupils were greatly dilated, but now the secretions of the salivary and lacrymal glands were diminished. In seven minutes, the dog lay quietly on the abdomen and thorax; and in thirteen minutes it fell over on the side. An endeavour was made to count the cardiac impulses, but, when the hand was placed over the heart, the tremors referred to became so greatly increased that it was impossible to distinguish the heart's impulse. It was not until thirty-eight minutes, that an attempt to count the heart's contractions was successful, and then it was found that the impulses occurred at the rate of 45 in ten seconds. At the same time, the respirations had a rate of 7 in ten seconds, and the pupils measured $\frac{17}{50} \times \frac{17}{50}$ths of an inch. In forty-eight minutes, the condition of the

dog had so far improved that, after some efforts, it rose on the limbs, and then lay down in a normal crouching attitude, with the head raised. Soon afterwards, it again got up and walked about the room, with only a little unsteadiness. In one hour and fifty-five minutes, the animal seemed to be perfectly well. On the following day, the dog was active, and in a perfectly normal condition. Nineteen days after the performance of this experiment, the same dog received, by subcutaneous injection, a dose of sulphate of physostigmia, only one-half as large as that from which it had recovered when atropia was also given; and the result was that death was produced in twenty-two minutes.*

Gentlemen, the details of these three experiments will serve, I trust, to convince you that atropia exerts a powerful counteracting influence upon the lethal action of physostigma. I am glad to be able to state that several experiments bearing on this antagonism have been performed by Dr. Bourneville of Paris, which have led to equally satisfactory results. The experiments which I have brought under your notice by no means represent the amount of evidence that may be advanced in support of this antagonism; for results similar to those I have described were obtained in a large number of other experiments. These additional experiments, however, were not undertaken for the mere purpose of increasing the amount of this evidence.

Limits to the Antagonism between Atropia and Physostigma.—As both atropia and physostigma possess a number of separate actions, it was not unreasonable to anticipate that several of them are not mutually antagonistic; and, therefore, that combinations of certain doses of the two substances may be administered whereby the non-antagonist actions will be produced in sufficient degrees of energy to be able to cause death. The possibility of a fatal result ensuing after the combined administration of the two substances in certain doses is also rendered probable by many facts which show that several of their actions are of a similar nature. When a dose not greatly above the minimum-lethal of the one is counteracted by a moderate dose of the other, these similar actions are not produced in sufficient intensity to become, even in combination, important toxic actions. When, however, a dose considerably above the minimum-lethal of the one substance is given along

* Full details of these, and other similar experiments, are contained in a paper by the author, in the *Transactions of the Royal Society of Edinburgh*, vol. xxvi, part III, 1870-71, pp. 529 713.

with a large dose of the other, the similar actions may be produced in such intensity as to assume the importance of lethal actions.

Guided by these considerations, I anticipated that the counteracting influence of atropia upon the lethal action of physostigma is successfully exerted only within a limited range of doses, and that this range may be determined by experimental research. The task of making this determination was undertaken because it seemed likely that results would thereby be obtained of the greatest interest and novelty, in connexion not only with this special instance of counteraction, but also with the general subject of physiological antagonism and its important and direct bearing on the principles of therapeutics.

In order to define the limits of the counteracting influence of atropia upon the lethal action of physostigma, three series of experiments were made. The chief objects of the first two of these were to ascertain the maximum dose of physostigma that can be successfully antagonised by atropia, and the range of doses of atropia that can successfully antagonise lethal doses of physostigma. In each series, a constant interval of time was maintained between the administration of the two substances; but in the first atropia was administered five minutes before physostigma, while in the second physostigma was administered five minutes before atropia. In both of these series, experiments were made, in the first place, with the minimum-lethal dose of physostigma; and, in combination with it, various doses of atropia were administered, ranging from one that was too small to prevent the lethal action, through a number that were able to prevent death, until a dose was found whose administration resulted in death. Similar experiments were made with a dose of physostigma one-and-a-half times as large as the minimum-lethal, then with one twice as large as the minimum-lethal, and so on, at the same rate of progression, until a dose was reached that was too large to be successfully antagonised by any dose of atropia.

The chief object of the third series of experiments was to ascertain within what limits of time between the administration of the two substances successful antagonism occurs. In the experiments of this series, a constant dose of physostigma was given along with various doses of atropia; and with each dose of atropia several experiments were made, which differed from each other by a difference in the interval of time between the administration of the two substances. On this plan, two sets of experiments were performed, in one of which atropia was given before physostigma, and in the other after it; and subsequently these two sets of experiments were connected together by

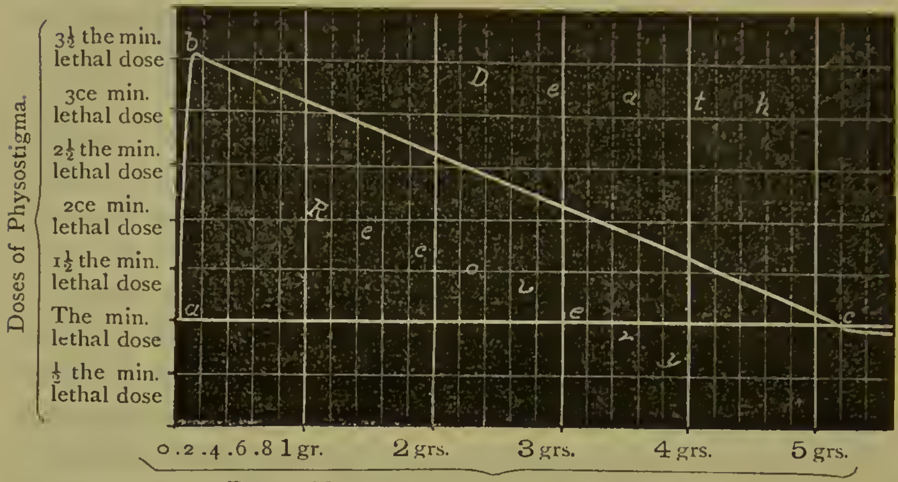
a third, in which atropia in various doses was administered simultaneously with the same dose of physostigma as was given in the two other sets of experiments. I found it necessary to make all the experiments of these three series on rabbits, as it was impossible to obtain a sufficient number of dogs or other convenient animal. The rabbits used were as nearly as possible three pounds in weight; but, when they were lighter or heavier than three pounds, a correction was made, so that each dose represented three pounds weight of animal. The two substances were administered by subcutaneous injection.

In the first series of experiments—where the atropia was administered five minutes before the physostigma—it was found that, when the minimum-lethal dose of physostigma was administered, 0.005 grain of sulphate of atropia is too small a dose to prevent death, but that 0 015 grain is sufficient to do so; and that with any dose ranging from 0.015 grain to 5.2 grains, the lethal action of this dose of physostigma may be prevented; while, if the dose of atropia be 5.3 grains or more, the region of successful antagonism is left, and death occurs. With one-and-a-half times the minimum-lethal dose of physostigma, successful antagonism was produced by doses of sulphate of atropia ranging from 0.02 to 4.1 grains; with twice the minimum-lethal dose of physostigma, with doses of sulphate of atropia ranging from 0.025 to 3.2 grains; with two-and-a-half times the minimum lethal dose of physostigma, with doses of sulphate of atropia ranging from 0.025 to 2.2 grains; with thrice the minimum-lethal dose of physostigma, with doses of sulphate of atropia ranging from 0.06 to 1.2 grain; and with three-and-a-half times the minimum-lethal dose of physostigma, with doses of sulphate of atropia ranging from 0.1 to 0.2 grain. Successful antagonism could not be obtained above this dose; and accordingly three-and-a-half times the minimum-lethal dose of physostigma is the largest quantity whose lethal action can be prevented in rabbits by atropia administered five minutes previously.

To aid your comprehension of these results, I have prepared a diagram (Diagr. 1) in which they are shown in a graphic form. In this diagram, the doses of atropia are represented by the distance, in a horizontal direction, from the perpendicular line forming the left margin; and they increase at the rate of two-tenths of a grain for every subdivision of the horizontal lines. The doses of physostigma increase from below upwards; the minimum-lethal dose being represented by the thick horizontal line; a dose one-and-a-half times as large as the minimum-lethal, by the thin horizontal line immediately above the

thick one ; a dose twice as large as the minimum-lethal, by the next thin horizontal line ; and so on until a line is reached near the top of the diagram, which represents a dose of physostigma three-and-a-half times as large as the minimum-lethal. The curved line, *a b c*, separates

DIAGRAM I.



Doses of Sulphate of Atropia (per 3 lbs. of animal).

the fatal experiments from those that terminated in recovery;* and accordingly the space enclosed by it represents a region in which recovery always occurs, while the space on its outside represents a region in which death always occurs. With these explanations, the results of the experiments will be rendered apparent by a mere glance at the diagram. It may again be pointed out that the more obvious of these results are, that the maximum dose of physostigma which, in rabbits, can be rendered non-lethal by atropia administered five minutes previously, is about three-and-a-half times the minimum-lethal dose; and that the range of doses of atropia which are able to render non-fatal various otherwise fatal doses of physostigma, diminishes as the dose of physostigma increases. The general nature of these results is well illustrated in the diagram by the triangular form of the region of recovery after lethal doses of physostigma (*a b c*), of which the apex, *b*, indicates the maximum antagonisable dose of physostigma ; and the gradual increase in breadth from the apex to the thick horizontal line, *a c*, the gradual increase in the range of doses of atropia that can prevent the

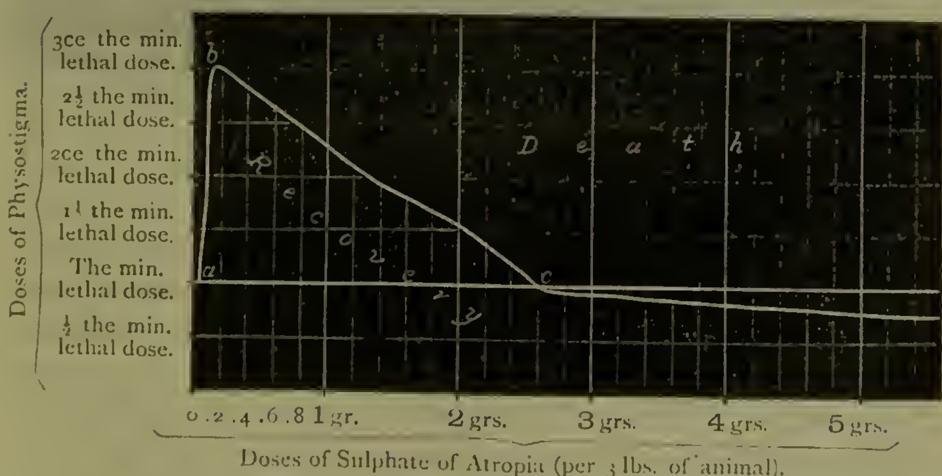
* In the diagrams exhibited during the lecture, the fatal experiments were marked by crosses, and the non-fatal by dots ; but this has not been done in the reduced copies that are here inserted, as the required space is wanting.

fatal effect of doses of physostigma diminishing from three-and-a-half times the minimum-lethal to the minimum-lethal.

The considerations which led me to anticipate that the counteracting influence of atropia upon the lethal action of physostigma is successfully exerted only within a definite range of doses, and that death may be produced when a lethal dose of physostigma, which is capable of being rendered non-lethal by atropia, is given in combination with a somewhat large non-lethal dose of atropia, also led me to anticipate that death may be produced by the combined administration of non-lethal doses of the two substances. I accordingly made some experiments in which half the minimum-lethal dose of physostigma was administered five minutes after various doses of atropia. It was shown by these experiments that death occurs if the dose of atropia be one that is equivalent to about ten grains per three pounds weight of animal, or a larger dose. This result appears a very remarkable one, when it is considered that successful counteraction is produced by much smaller doses of atropia against the poisonous action of doses of physostigma greatly in excess of the minimum-lethal, and that the minimum-lethal dose of sulphate of atropia itself is about twenty-one grains. It, however, may be simply explained by supposing some action or actions of both physostigma and atropia between which there is no mutual counteraction.

The second series of experiments—in which, as you may remember, the physostigma was administered five minutes *before* the atropia—yielded essentially the same results as the first series, excepting that the region of successful antagonism was found to be a more limited one.

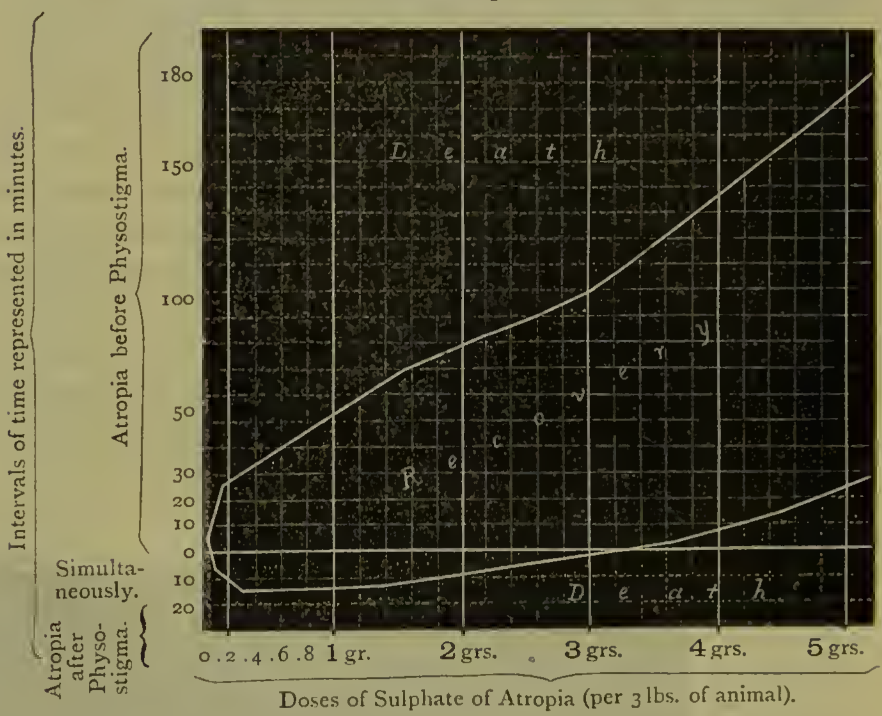
Diagram 2.



This difference is apparent when the diagramatic representation of the experiments of the second series (Diagr. 2) is compared with that of the first (Diagr. 1). In both series, the general result was obtained that the range of the doses of atropia capable of preventing the lethal action of physostigma diminishes according as the dose of physostigma is increased.

In the third series of experiments, I endeavoured to determine what influence the interval of time separating the administration of the two substances exerts upon the production of successful antagonism. I contented myself with making this determination in the case of one constant dose of physostigma (one-and-a-half times the minimum lethal), given in conjunction with doses of atropia ranging from the

DIAGRAM 3.

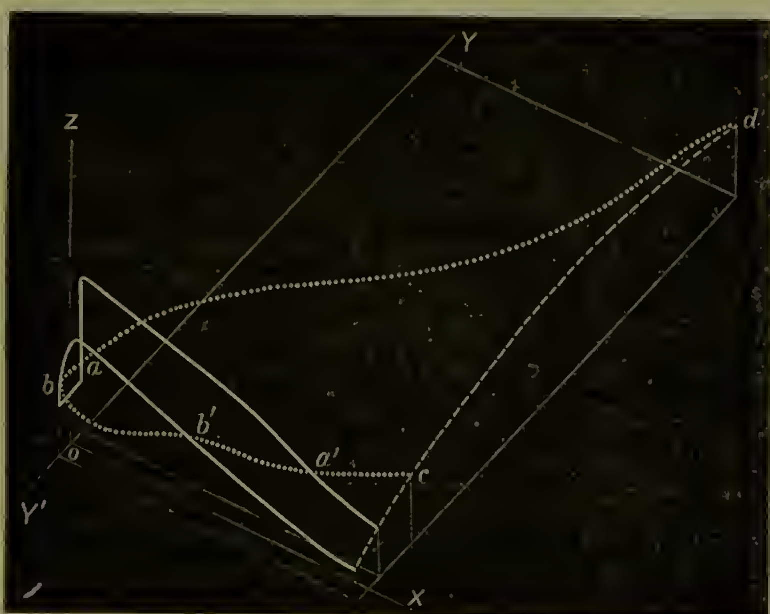


one-hundredth of a grain to five grains. The general results of this series are represented in the diagram (Diagr. 3). Without occupying your time with details, I would merely point out that successful antagonism was found to occur with a greater range of doses of atropia, and with a greater range of intervals of time, when atropia is given before physostigma, than when it is given after it (shown in the diagram by the much greater extent, laterally and vertically, of the region of recovery above the thick horizontal line representing simultaneous admi-

nistration, than below that line). In the latter case, the length of the intervals of time is obviously limited by there being a limitation to the time within which the dose of physostigma that was given itself produces death. In the former case, the intervals are not subject to a similar curtailment, seeing that the doses of atropia administered were all considerably below the minimum-lethal dose.

In the three series of experiments that have now been described, I have pointed out the limits of antagonism—firstly, when atropia is administered five minutes before physostigma; secondly, when atropia is administered five minutes after physostigma; and, thirdly, when atropia in various doses is administered at various intervals of time before and after one-and-a-half times the minimum-lethal dose of physostigma. You will observe that in each series, of the three quantities (namely, dose of physostigma, dose of atropia, and interval of time),

Diagram 4



In this diagram, doses of physostigma are indicated by the distance (parallel to the axis of z) from the plane, YOX; doses of atropia, by the distance (parallel to the axis of x) from the plane, ZOY; and intervals of time between the administration of the two substances, by the distance (parallel to the axis of y) from the plane, ZOX, points on the Y side of this plane indicating atropia administered *before* physostigma, and points on the Y′ side indicating atropia administered *after* physostigma. I am indebted to my friend Dr. Crum Brown for the drawing from which this woodcut has been made.

only two vary; and, therefore, that the results of any one series may be represented by a diagram on a plane, as in the diagrams I have brought under your notice. A combined representation of the results

of the three series of experiments, involving as it does three variable quantities, will, however, be best effected by a model in three dimensions, such as I now show you. Diagram 4 is an orthogonal projection of this model, in which the three variables are represented on a scale somewhat different from that of Diagrams 1, 2 and 3; but this difference does not cause any difficulty in the recognition of the corresponding parts. The continuous line, *a a'*, represents the boundary of the region of recovery in the experiments where atropia was administered five minutes *before* physostigma (Series 1); the continuous line, *b b'*, the boundary of this region where atropia was administered five minutes *after* physostigma (Series 2); and the dotted line, *c a' b' b a d*, the boundary of this region where atropia was administered in various doses and at various intervals of time before and after one-and-a-half times the minimum-lethal dose of physostigma (Series 3). It is obvious that these lines lie upon a curved surface, on whose one side every point represents conditions leading to death, and on whose other side every point represents conditions leading to recovery. The surface, of course, cannot be fully known from the three sections of it that have been obtained by these experiments. It could be known only by greatly increasing the number of the experiments, so as to obtain a number of other curves parallel to and on either side of *b b'* and *a a'*, and of horizontal sections parallel to and below and above *c a' b' b a d*. To obtain a sufficient number of such curves, however, the labour and expenditure of time would be very great, seeing that so large a number of experiments as two hundred and seventy-six were made in order to obtain the curves represented in the diagram. Besides, a tolerably accurate conception of the form of the curved surface may be gained from the curves of the three series of experiments that have been made.

The region included within this curved surface represents every possible variation in the doses of atropia and physostigma, and in the intervals of time separating the administration of the two substances, that is compatible with the production of successful antagonism between physostigma and atropia. Its existence shows us how an investigation on antagonism may lead to very fallacious results, even when every care has been taken in obtaining a large amount of experimental data. I have already pointed out that, almost without exception, the instances of lethal antagonism asserted to exist cannot be regarded as certainly established, because sufficient care has not been taken in proving that recovery took place after an undoubtedly lethal dose of

one of the substances concerned. In attempting to *disprove* the existence of any asserted instance of lethal antagonism, a fallacy of equal importance may originate from ignorance of the fact that the antagonism does not necessarily occur throughout an unlimited range in the doses of the two substances, or in the intervals of time separating their administration: in short, that there is a region of death as well as a region of recovery in connection with probably every instance of lethal antagonism. Unless, therefore, the factors I have mentioned be greatly varied in a large series of experiments, it cannot be positively asserted that the antagonism does not exist. It appears to me that the fallacy to which I have now drawn your attention, has not been sufficiently attended to in much that has recently been written on the subject of antagonism.

Bearing of Antagonism between Active Substances on Therapeutics.—An eminent authority in pharmacology has recently published the statement, that the only method by which the injurious action of a poison can be made to terminate is by the employment of such means as will cause or hasten the elimination of the poison. This statement, fortunately, does not accurately describe our remedial resources. The existence of so undoubted an example of physiological antagonism as that which I have brought before you shows that the toxic action of a morbific agent may be directly opposed by the physiological action of an antidote or remedy; and, therefore, that recovery may be produced not only by removing the cause of the abnormal conditions, but likewise by directly influencing these abnormal conditions themselves in such a manner as to cause their return to a normal state.

It does not seem, however, that, in order to effect this return, the dose of the remedy must necessarily be increased in proportion to that of the morbific agent. This general principle has hitherto been somewhat vaguely recognised as a guide for treatment. The greater the severity of the symptoms, the greater the need for administering the antidote in large doses. When it is remembered that the action of poisons—whether these be the known substances with which toxicology is concerned, or those unknown substances on which the symptoms of many diseases are dependent—is rarely a simple one, but a series of independent actions directly involving many structures, and that the action of the antidote or remedy is in like manner the aggregate of several independent influences, we at once see how improbable it is that each of these several actions should be mutually antagonistic. In the case of the antagonism between atropia and physostigma,

only a limited number of the different actions produced by each substance are of an opposite, and therefore counteracting kind ; while others of these actions—either of a similar or of a different nature—are not mutually counteracting. Successful antagonism occurs when the doses are so proportioned that the non-counteracting actions are not permitted to acquire an undue prominence. When, however, they are permitted to acquire this prominence, death, and not recovery, occurs ; and this result may be induced by an increase, beyond certain proportional limits, of the dose either of atropia or of physostigma. When the dose of physostigma is a large one, therefore, we find that a comparatively small and not a large dose of atropia is the proper one to administer; and, when the dose of atropia is a large one, we find that it can successfully antagonise only a small, and not a large, dose of physostigma.

I cannot avoid thinking that, were our knowledge of the conditions produced by disease as accurate as that of the conditions produced by many active substances, it would, for similar reasons, be found that a remedy which exerts so perfect a counteraction to a disease as to be able to prevent its fatal effect, would aid, and not prevent, the lethal action, when given in a somewhat large dose, even when this dose is considerably below the minimum-lethal. Just as we have seen that the actions of atropia which are not employed in counteracting those of physostigma, may increase the fatal power of a dose of the latter substance to such an extent that death occurs, even when the dose of neither substance is of itself sufficient to cause death.

The occurrence of this anomalous result is well worthy of consideration for another reason. The symptoms that are produced by a dose of physostigma *slightly* below the minimum-lethal are of so serious a character, that it is impossible to predict from their evidence alone whether death or recovery will occur. This can only be done by previously defining the minimum-lethal dose ; and, unless this precaution be taken, the greatest errors may arise in judging of the effects of antidotes. Do we not find an analogy between this cause of error and that which frequently characterises the inductions of therapeutists ? A disease that produces symptoms of the most serious import, does not necessarily terminate in death, even although this termination be a frequent one. The *dose of disease* present may not be so large as a minimum-lethal one, and still the symptoms may be sufficiently urgent to induce us to consider that they are caused by such a dose. If a remedy be applied in these circumstances—and, in the present state of

our knowledge, they are probably always present—what surety can there be that the remedy has cured the disease? or that any remedy which may have been employed is not an efficient counteragent to its fatal effect? or even that the so-called *vis medicatrix naturæ* is not alone sufficient to counteract its lethal action? In presence of these uncertainties in reference to the exact degree of diseased action which is necessary to produce death—the exact dose of the disease that constitutes the minimum-lethal—there is little cause for wonder that scepticism regarding the power of remedies should exist, or that the unfortunate irrationalism of an indiscriminate expectancy should be revived as a therapeutic dogma.

I venture to think, however, that even the few facts which I have this evening brought before you are sufficient to show that a series of abnormal actions which, if uuchecked, would inevitably terminate in death, may be so modified by an antidote or remedy, that the tendency to death is averted, and recovery produced. The existence of such an antagonism as that between atropia and physostigma encourages the hope that the power of directly counteracting disease is far from unattainable; and it supplies a strong incentive to efforts designed to determine the conditions of disease and the actions of remedies with an exactitude sufficient to show how the remedial action may be applied as a counteracting influence to the diseased condition.